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Letter to the Editor. Phase III randomized controlled trials are essential to properly evaluate the role of radiotherapy in WHO grade II meningioma

Jenkinson, Michael D ; Weber, Damien C ; Haylock, Brian J ; Sherratt, Frances C ; Young, Bridget ; Weller, Michael ; Bulbeck, Helen ; Culeddu, Giovanna ; Hughes, Dyfrig A ; Brain, Alice ; Das, Kumar ; Preusser, Matthias ; Francis, Priya ; Gamble, Carrol

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Neurosurgical Forum

LETTERS TO THE EDITOR

Is the serum glucose/potassium ratio a reliable prognostic factor for aneurysmal SAH?

TO THE EDITOR: We studied with keen interest the article by Fujiki et al.¹ regarding the role of the serum glucose/potassium ratio in predicting the outcome of aneurysmal subarachnoid hemorrhage (SAH) (Fujiki Y, Matano F, Mizunari T, et al: Serum glucose/potassium ratio as a clinical risk factor for aneurysmal subarachnoid hemorrhage. *J Neurosurg* [epub ahead of print November 17, 2017. DOI: 10.3171/2017.5.JNS162799]). We commend the authors for their attempt to revisit this question because biomarkers for predicting poor prognosis following aneurysmal SAH have not yet been established. However, we would like to bring forth a few issues in this article that need further consideration. In their retrospective study design involving 565 subjects, they did not mention any inclusion or exclusion criteria. In their patient selection, there was no account of any pre-existing cause of hyperglycemia, which can be attributed to diabetes, metabolic syndrome, or insulin resistance. The drug status on admission—that is, taking oral hypoglycemic agents, insulin, or beta blockers—was not mentioned. The authors did not mention hypertensive status on admission or BMI in their summary of patient characteristics, which could have been potential confounders of a poor outcome.

There was no time cutoff from SAH to admission. The range of time from SAH to admission was 1 hour to 16 days (mean time 20.1 ± 19.07 hours). Hence, the time from SAH to admission could be an independent factor affecting prognosis, with late admissions faring worse. Moreover, the authors did not mention whether it was a single value or a mean value of serum glucose or potassium estimation at the time of admission. Also, there was no account of those patients who were normoglycemic at admission but later developed hyperglycemia. The authors report that they used sliding scale insulin for post-admission hyperglycemia control, but it would have been insightful to know the insulin dosage, which could highlight the degree of hyperglycemia and metabolic stress. The study fails to answer a pertinent question, that is, whether the glucose/potassium ratio is associated with the risk of vasospasm/delayed cerebral injury. Moreover, no correlation of the serum glucose/potassium ratio with the Glasgow Outcome Scale (GOS) score at 3 months was

assessed, which misses out on patients who could have delayed recovery.

Finally, we would like to congratulate the authors on bringing to light an interesting scientific issue. Their article lays the groundwork for a larger prospective study design to evaluate these biomarkers in aneurysmal SAH to aid in treatment policy decisions.

Ravi Sharma, MBBS

Manoj Phalak, MCh

Prateek Sharma, MBBS

All India Institute of Medical Sciences, New Delhi, India

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Disclosures

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Correspondence

Manoj Phalak: manojphalak@yahoo.com.

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Response

Thank you for your helpful comments regarding our article.

All patients with acute endogenous SAH (confirmed by CT or lumbar puncture) were eligible for study participation and were included if they or their health care decision surrogate provided consent. Patients with traumatic SAH and cardiopulmonary issues on arrival were excluded. Additionally, pre-existing hyperglycemia was defined by a history of diabetes, the use of oral hypoglycemic agents, the use of insulin, and an HbA1c value > 7.0 . Among the 565 treated patients, 46 had these conditions of pre-existing hyperglycemia. We found that 34 patients were using oral hypoglycemic agents, 3 were using insulin, and 5 were using beta blockers. With regard to the hypertensive status and BMI of the patients, we did not find a significant correlation between a poor outcome (GOS scores 1–3) and these factors.

As you mentioned, for patients with severe SAH, the time from SAH to admission can be very important for deciding prognosis. However, patients with low-grade SAH, such as those who presented with mild headache, tended to undergo a late checkup at the hospital, resulting in a late admission. Thus, the data were uncorrelated with the time to admission. We apologize for not mentioning this information, but a single value of serum glucose or potassium was considered at the time of admission.

Ten patients were normoglycemic at the time of admission but later developed hyperglycemia. Among these 10 patients, 7 (70.0%) had poor outcomes (GOS scores 1–3). However, the number of patients was not high enough to conclude a correlation with a poor outcome. Nevertheless, this situation should be considered.

With regard to the insulin dose, we believe that your point would have been insightful if we could show a correlation. However, we think that it is difficult to judge whether a patient already has diabetes or whether the shock from SAH has caused hyperglycemia because some patients with diabetes who had not been diagnosed could have been included. Sixteen patients used sliding scale insulin for post-admission hyperglycemia control, and the insulin dose was 4–52 units (mean 22.4 ± 16.0 units). Among 8 patients (50.0%) with poor outcomes (GOS scores 1–3), 5 needed insulin doses over 30 units.

We are currently working on another paper about the association of the glucose/potassium ratio with the risk of vasospasm/delayed cerebral injury, and this paper will be submitted soon. We hope that this paper will provide further clarification.

With regard to your last point, we have not provided information on that paper. However, we did analyze the correlation between the serum glucose/potassium ratio and GOS score at 1 year after discharge in 413 patients. Based on the estimation of the GOS score at 1 year after discharge, 180 patients (43.6%) were considered to have poor outcomes (GOS scores 1–3). There was a significant correlation between poor outcomes at 1 year after discharge and the serum glucose/potassium ratio. This finding indicates that we included patients who had delayed recovery.

Again, thank you for your helpful review of our article.

Yu Fujiki, MD

Fumihiko Matano, MD, PhD

Takayuki Mizunari, MD, PhD

Yasuo Murai, MD, PhD

Kojiro Tateyama, MD, PhD

Kenta Koketsu, MD, PhD

Asami Kubota, MD

Shiro Kobayashi, MD, PhD

Hiroyuki Yokota, MD, PhD

Akio Morita, MD, PhD

Nippon Medical School, Tokyo, Japan

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A nonsignificant trial result does not mean that two procedures are equal

TO THE EDITOR: Vieira et al.¹ contribute to the accumulating evidence on the commonly performed procedure of decompressive craniectomy by reporting the results of their randomized controlled study comparing 2 surgical techniques for decompressive craniectomy (DC): with watertight duraplasty and without watertight duraplasty (Vieira E, Guimarães TC, Faquini IV, et al: Randomized controlled study comparing 2 surgical techniques for decompressive craniectomy: with watertight duraplasty and without watertight duraplasty. *J Neurosurg* [pub ahead of print November 17, 2017. DOI: 10.3171/2017.4.JNS152954]).

Although one must greatly appreciate such randomized controlled trials with blinded evaluation of outcomes, there are a few methodological flaws in the trial. The authors give the impression that the experimental procedure is safe and hence equivalent to the traditional watertight cranioplasty. They come to the conclusion that rapid-closure DC without watertight duraplasty is a safe procedure and that it is not associated with a higher incidence of surgical complications. Assuming that a procedure is equivalent or non-inferior to another procedure just because there was no statistically significant difference is fundamentally wrong. Failure to reject the null hypothesis that the experimental procedure is not superior to the control procedure should not automatically prompt one to accept the null hypothesis and conclude that both procedures are equivalent in terms of safety.

In situations where one anticipates that one procedure is likely to be nearly equivalent to the other, as in the present case, a non-inferiority trial design should be used.

The authors describe a composite outcome of several complications, including CSF leak, subgaleal collection, and infective complications, as the primary outcome. The sample size should have been calculated to power the trial to find the primary outcome. However, the authors calculated sample size to find a significant difference in the duration of the surgery, which resulted in extremely low power to detect superiority in terms of complications. A retrospective calculation shows that the trial had only 5% power to detect a statistically significant difference for the primary outcome.

Consider a hypothetical example in which the control arm has only 1 complicating event compared to the same 5 complications that occurred in the experimental arm. The trial would still have shown no statistical significance!

TABLE 1. Hypothetical example

Trial Arm	Complications	No Complications	Total
Control (watertight)	1	27	28
Experimental (non-watertight)	5	22	27
Total	6	49	55

The Fisher exact test statistic value is 0.101181 (not significant, $p > 0.05$).

(See Table 1.) Hence it is not correct to conclude that both arms are equal in terms of primary outcome.

Moreover, the safety concern that there could be more cortical damage when one has to release adhesions at the time of a future cranioplasty procedure still remains. The authors have proven that closure without watertight duraplasty is faster and cheaper—but not necessarily safe.

Gopalakrishnan Madhavan Sasidharan, MCh

Jawaharlal Institute of Post-graduate Medical Education and Research,
Pondicherry, India

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The authors report no conflict of interest.

Correspondence

Gopalakrishnan Madhavan Sasidharan: gopalakrishnanms@gmail.com.

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Response

We appreciate the opportunity to respond to the comments by Dr. Sasidharan. Indeed, the small number of patients in our study diminishes the impact of our results, as we state in the *Discussion* section of our article. Usually, when a rapid-closure (non-watertight dural closure) DC is performed, 3 concerns come to mind: infection, CSF leak, and adhesion/scarring between the cerebral parenchyma and the pericranium. Regarding the risk of infection, in our study, the DC with watertight dural closure had a significantly longer surgical time when compared to the rapid-closure (non-watertight) DC (132 vs 101 minutes). Several studies have shown that longer surgeries are associated with a higher incidence of complications, particularly infectious complications.^{2,4,5} Surgeries lasting more than 120 minutes were associated with a 4-fold increased risk of surgical site infection.¹

In our study, overall complications were more common in the control group (with watertight dural closure, 5 cases) and not in the rapid-closure group (4 cases), as Dr. Sasidharan points out. The incidence of CSF leak and subgaleal fluid collections (possibly representing the occurrence of CSF leaks contained by the skin closure) was also higher in the watertight dural closure group. Once the arachnoid is intact, there is no increased risk of CSF leaks. Moreover, attempts to achieve watertight closure may lead to small defects on suture lines, causing a “one-way valve” effect that could potentially facilitate the development of CSF leakage. Güresir et al.³ described a DC procedure that is similar to the one we used in our study. With a total of 341 procedures, they concluded that the rapid-closure

technique did not increase the incidence of CSF leak, infection, and/or healing problems.

Regarding cortical adhesions, after performing a rapid-closure DC, the exposed brain parenchyma stays in contact with the pericranium, which usually is dissected along with the myocutaneous flap during opening. Pericranium is widely accepted as an autologous graft when performing watertight dural closure after any neurosurgical procedure. It is expected that the same degree of adhesion and scarring between the brain parenchyma and pericranium will occur, whether watertight duraplasty is performed or not. When performing cranioplasty, once the edges of the craniotomy are found, the myocutaneous flap can be easily dissected from this neo-formed fibrous layer that covers the brain parenchyma without pial injury. There is no need to expose the parenchymal surface. Güresir et al., in a retrospective analysis of 196 cranioplasties after rapid-closure DC, found no higher incidence of complications.³

Eduardo Vieira, MD

Igor V. Faquini, MD

Nivaldo S. Almeida, MD

Hildo R. C. Azevedo-Filho, Msc, PhD, FRCS

Hospital da Restauração, Recife, Brazil

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Low ICP and normal tension glaucoma: optic nerve damage due to barotraumatic factors, failure of CSF dynamics, or both?

TO THE EDITOR: We read with great interest the article by Gallina et al.² (Gallina P, Savastano A, Becattini E, et al: Glaucoma in patients with shunt-treated normal

pressure hydrocephalus. *J Neurosurg* [epub ahead of print November 17, 2017. DOI: 10.3171/2017.5.JNS163062]. We appreciate the authors' study and their efforts to explore the role of low intracranial pressure (ICP) in the pathogenesis of normal tension glaucoma (NTG). However, we feel that an issue described in their paper deserves further discussion.

As discussed by the authors, several studies have provided clinical evidence in support of the theory that reduced ICP may play a role in the pathogenesis of NTG.¹ In line with this theory, they demonstrate that patients whose ICP has been lowered following ventriculoperitoneal shunt placement, as treatment for normal pressure hydrocephalus, are almost 40 times more likely to suffer from NTG than elderly Italian patients without hydrocephalus.² The mechanisms most commonly proposed to explain the contribution of low ICP and thus a high trans-lamina cribrosa pressure difference (intraocular pressure – ICP) to glaucoma are direct strain on the lamina cribrosa, impairment of axonal transport, and altered blood flow.¹ The authors cite one of our papers,¹⁰ which focused on the possible role of cerebrospinal fluid (CSF) circulatory dysfunction in NTG, and argue against our hypothesis stating that “the finding that NTG occurs in patients whose CSF clearance was forced more strongly by the sink action of the diversion does not support, as already noted, a pressure-independent pathogenetic hypothesis, which focuses on the accumulation of toxins at the level of the optic nerve due to failure of CSF dynamics.”² For the reasons set forth below, we respectfully disagree with this statement.

Evidence in support of our viewpoint comes from a recent dog study by Hou et al.³ During CSF shunting from the brain ventricle, the intraventricular ICP gradually decreased in a linear fashion together with the optic nerve subarachnoid space (SAS) pressure.³ But when the ICP fell below a critical breakpoint, optic nerve SAS pressure remained constant despite further ICP decline.³ These authors interpreted this as a sign of CSF communication arrest between the intracranial and optic nerve SAS.³ Indeed, when ICP drops too low, the breakpoint is reached and CSF flow stops.³ This means that the ICP is too low for CSF to freely flow through the optic canal.³

Intriguingly, the findings by Hou et al.³ may bring together two seemingly very different theories of glaucoma pathogenesis. Berdahl and Allingham,¹ as well as others,⁹ have suggested that the lower ICP reported in glaucoma patients could play a role in the pathogenesis of the disease through a higher pressure difference across the lamina cribrosa, influencing the physiology and pathophysiology of the optic nerve head. However, it should be noted that the clinical retrospective and prospective studies of CSF pressure in patients with glaucoma have taken the lumbar CSF pressure measurement as a surrogate for the retrolaminar CSF pressure¹ and that the true CSF pressure behind the lamina cribrosa is not known.⁷ Furthermore, two recent studies did not confirm lower ICP in NTG patients.^{5,8} Killer et al.⁴ suggested that open-angle glaucoma may be due to the sequestration of CSF within the terminus of the optic nerve SAS, creating a stagnant region accumulating substances toxic to the adjacent optic nerve head. Wostyn et al.¹⁰ proposed that decreased ICP and an optic nerve

sheath compartment syndrome could be seen as sequential steps in the disease process of NTG. The dog study by Hou et al.³ indeed suggests that if the ICP is too low, CSF flow from the intracranial SAS into the optic nerve SAS stops and CSF drainage from the optic nerve SAS is interrupted as well, creating a CSF compartment syndrome. Compartmentation of the optic nerve SAS seems to be associated with a narrower optic canal cross-sectional area in NTG patients.⁶

Given the above considerations and given that both the hydrostatic pressure and the dynamics of CSF may be of great importance for the physiological stability of the optic nerve,¹¹ we believe that the pressure gradient with shear stress at the site of the lamina cribrosa may be accompanied by another mechanism, namely toxicity of non-recycled CSF around the optic nerve.

Peter Wostyn, MD¹

Veva De Groot, MD, PhD²

Debby Van Dam, PhD^{3,4}

Kurt Audenaert, MD, PhD⁵

Peter Paul De Deyn, MD, PhD^{3,4,6}

Hanspeter Esriel Killer, MD⁷

¹PC Sint-Amandus, Beernem, Belgium

²Antwerp University Hospital, Antwerp, Belgium

³Laboratory of Neurochemistry and Behavior, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium

⁴University of Groningen and University Medical Center Groningen, Groningen, The Netherlands

⁵Ghent University Hospital, Ghent, Belgium

⁶Middelheim General Hospital (ZNA), Antwerp, Belgium

⁷Kantonsspital Aarau, Aarau, Switzerland

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Correspondence

Peter Wostyn: wostyn.peter@skynet.be.

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Response

We are pleased regarding the letter by Wostyn et al. because it gives us the possibility of critically checking our contention that a lowering of ICP underlies optic nerve damage in shunted normal pressure hydrocephalus. Those results support the role of changes in intraocular pressure and ICP gradient across the lamina cribrosa in the pathophysiology of NTG.²⁰

The arguments by Wostyn et al. descend from experimental findings in dogs,⁷ in which CSF circulation at the level of the optic nerve SAS is halted when ICP falls below a critical breakpoint value. According to Hou et al.,⁷ this would involve CSF segregation, thus preventing the supply of nutrients to, and the disposal of waste molecules from, the so-called optic nerve chamber.^{10,11} Wostyn et al. disputed that these findings would put into question our inference that the failure of CSF dynamics cannot explain the occurrence of NTG in precisely those patients with lower opening pressure valve values, where CSF clearance was forced by the stronger sink action of the diversion. Consequently, we argued that a pressure-independent pathogenetic hypothesis based on the accumulation of toxins at the level of the optic nerve due to CSF circulation failure²¹ cannot apply to our data because a higher CSF clearance would prevent stagnation of CSF.

Admittedly, because of the obvious anatomical-physiological differences, it is difficult to straightforwardly translate the results obtained in dogs into human beings. However, dogs have been widely used to study CSF hydrodynamics since the classic work of Dandy and Blackfan.⁴ Therefore, it was tempting to play along, and we noted that our NTG patients underwent a lowering of ICP within the ICP-dependent zone identified by Hou et al.,⁷ where the intraventricular values decreased linearly with optic nerve SAS pressure. As a consequence, our patients experienced optic nerve damage even though the hypothetical arrest of communication between the intracranial and optic nerve SAS would not have occurred yet.

Recent anatomical evidence supports the notion that free circulation of CSF within the optic canal in humans may be hampered,^{16,17} leading to compartmentalization of

the SAS within the canalicular portion and the accumulation of toxins, possibly causing NTG.¹¹ Liugan et al.¹⁶ revealed the fibrous components within the optic canal and their relationship with the optic nerve SAS, which are suggestive of a valve mechanism at work in CSF sequestration.¹² A bony bottleneck responsible for CSF circulatory dysfunction was advocated by Pircher et al.,¹⁷ who showed that the optic canal, as measured in the coronal plane at the orbital opening, is smaller in NTG patients than in controls. These results were paralleled by MRI data showing lower CSF flow between the intracranial cavity and optic nerve SAS in NTG patients compared to that in healthy controls.³ Overall, these findings shift the anatomical-physiological site of NTG pathogenesis far from the lamina cribrosa, the structure where an increased pressure gradient between the intraocular and intracranial compartments would act and damage the optic nerve.²⁰ Moreover, Wostyn et al. put forward two recent studies^{14,18} that reported no ICP decrease, as measured by lumbar puncture, in white NTG patients, suggesting that the current view²⁰ of the trans-lamina cribrosa gradient hypothesis should at least be reconsidered. However, Pircher et al.¹⁸ performed a retrospective study without a control group, which limits the generalizability of their results. Moreover, these studies^{14,18} share two more weaknesses: 1) lumbar CSF pressure is not accurate enough to extrapolate ICP around the optic nerve,⁹ and 2) both involved white patients—which could explain the discrepancy between their results and those of Ren et al.,¹⁹ who studied an Asian population. Nonetheless, recent advances in ultrasound technology have allowed higher-resolution images of the optic nerve SAS to be generated, enabling more detailed measurements and increased power to predict CSF pressure at that level.¹⁵ Liu et al. demonstrated that NTG patients had a significant smaller optic nerve SAS than healthy controls, a finding that was indicative of lower CSF pressure and suggestive of an abnormally high trans-lamina cribrosa pressure difference in the NTG group.¹⁵

In fact, the pathophysiology of NTG remains incompletely understood. Both the barometric and the CSF dynamics failure hypotheses are supported by bodies of evidence. Intriguingly, Wostyn et al. propose a reconciliation between the two theories and advance a stepwise nature for the disease. Wishing to follow the advice from Wostyn et al., we plan to check the possible concomitance of some features supporting the CSF compartment syndrome at the optic nerve SAS in our normal pressure hydrocephalus patients whose ICP was lowered by a CSF shunt. We will simply look at possible differences in the size of the optic canal¹⁷ between NTG and no-NTG groups. If the mechanism involved in NTG occurrence in these patients is related to the lowering of ICP, as we have argued, a narrowing of the optic canal should not be expected. Indeed, the trans-lamina cribrosa pressure difference hypothesis assumes free communication between the intracranial CSF spaces and the lamina cribrosa, which is, in fact, posteriorly displaced in NTG,¹³ while a canalicular bottleneck would limit the transmission of ICP through the SAS. It is worth noting that severe papilledema and poor visual function were associated with a larger optic canal in 69 patients with idiopathic intracranial hypertension,² while

a smaller size was associated with the less affected side in 8 patients with asymmetrical papilledema.¹ Further clinical studies may also assess possible age differences among NTG patients in relation to optic canal size. In this regard, it has been shown that optic canal volume decreases with aging.⁶ Pircher et al.¹⁷ could not detect a significant correlation between optic canal size and age in either the NTG group or the control group. However, it should be noted that their samples were dimensionally inadequate to appreciate small effect sizes. For the sake of speculation, we considered the data of Pircher et al.¹⁷ and found that their youngest (age < 60 years) NTG patients had a smaller optic canal size than those measured in their oldest (age > 80 years) NTG patients. The opposite was true for their controls, in whom the size of the optic canal of the oldest subjects was narrower than that measured in the youngest group. These inverse correlations between NTG and controls were especially valid for males. Therefore, the question is far from being settled, especially if ethnic differences come into play. Notably, optic canal measurements in Chinese patients showed larger cross-sectional areas compared to those in whites.^{8,17} Nevertheless, if an anatomical narrowing of the optic canal predisposes to an impairment of CSF flow in the optic nerve SAS, which can now be assessed in a noninvasive manner,³ CSF compartmentalization would occur early. As a consequence, the damage to the optic nerve would appear in the absence of intracranial hypotension, which is an age-related process.⁵ On the other hand, in the presence of a relatively large optic canal, NTG occurrence might be expected to be a process related to aging. In this light, the temporal dimension and anatomical interindividual variation at the level of the optic canal may ultimately make someone more liable to either barometric damage at the lamina cribrosa or to stagnation of toxic substances within the compartmentalized optic canal SAS. Undoubtedly, much experimental and clinical knowledge is still needed to understand which one of these mechanisms underlies NTG and if they operate together or alternatively.

Pasquale Gallina, MD
Nicola Di Lorenzo, MD
Alfonso Savastano, MD
Stanislao Rizzo, MD
Berardino Porfirio, MD
University of Florence, Italy

Antonio Scollato, MD
University Hospital "Ospedali Riuniti" of Trieste, Italy

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Phase III randomized controlled trials are essential to properly evaluate the role of radiotherapy in WHO grade II meningioma

TO THE EDITOR: We read the study by Rogers et al.⁷ (Rogers L, Zhang P, Vogelbaum MA, et al: Intermediate-risk meningioma: initial outcomes from NRG Oncology RTOG 0539. *J Neurosurg* 129:35–47, July 2018). Intermediate-risk meningiomas were defined as those with a higher recurrence rate and include WHO grade II meningiomas (Simpson grades I–III) that had undergone gross-total resection (GTR) and any recurrent WHO grade I meningioma, regardless of the extent of resection. Despite the relative radioresistance of meningiomas, radiotherapy remains the only available adjuvant therapy for these tumors; in WHO grade II meningioma, there is a lack of class I evidence for the role of early adjuvant radiotherapy.⁵

Treatment decisions (i.e., adjuvant radiotherapy vs no adjuvant radiotherapy) after surgery currently factor in tumor location, the patient's pretreatment characteristics, and the willingness of the surgeon to reoperate if there is a recurrence.⁴ Tumor recurrence undoubtedly has an impact on patient quality of life, and, if adjuvant radiotherapy can deliver prolonged control with low risk, it should be considered in the multimodality management of WHO grade II meningiomas. RTOG 0539 was a phase II nonrandomized study with a primary endpoint of 3-year progression-free survival and included 36 patients with GTR grade II meningiomas who received postoperative radiotherapy; of these patients, one patient's disease progressed and another patient died of the disease, resulting in a 3-year local failure rate of 4.1%. It is reassuring to note that the early adverse events (from radiotherapy) were limited to Common Terminology Criteria for Adverse Events grade 1 or 2 (mainly dermatological) with no severe events.

Neurosurgeons have been historically skeptical about adjuvant radiotherapy, citing concerns about the risk of late cognitive decline, which is also a concern for patients.⁸ It is also reassuring that the RTOG 0539 study reported that mild memory decline affected only a small number of patients, although detailed cognitive assessment was not performed. Likewise, another phase II trial performed by the European Organisation for the Research and Treatment of Cancer (EORTC 22042-26042) did not show any cognitive impact after high-dose radiotherapy and similar control rates (D.C. Weber, personal communication). The relatively mild adverse events may be attributable to better radiotherapy planning techniques that minimize the radiotherapy dose to normal brain;¹ however, it is important to emphasize that both phase II studies had only 3 years of follow-up and later meningioma recurrence may occur.

The lack of a control arm is the main limitation of the study, and neurosurgeons are likely to remain skeptical about adjuvant radiotherapy for GTR WHO grade II meningioma. Nevertheless, the favorable adverse event profile of radiotherapy supports the continued enrollment

into open phase III studies. The Radiation versus Observation following Surgical Resection of Atypical Meningioma (ROAM)/EORTC 1308 trial (ISRCTN71502099) is a multicenter, phase III, randomized controlled trial that will answer the following question: In patients who have undergone GTR of atypical meningioma, does early adjuvant radiotherapy reduce recurrence compared to active monitoring?³ The study is open across the United Kingdom, Europe, Australia, and New Zealand (<http://roam-trial.org.uk>), with 44 sites open (63 planned) and 36 patients randomized (190 planned). The study is powered to detect an absolute reduction in recurrence rate from 40% (control arm) to 20% (radiotherapy arm) at 5 years and importantly will collect data on quality of life and neurocognitive function and assess whether adjuvant radiotherapy is cost-effective. Studies of intervention versus monitoring can pose a recruitment challenge since clinicians and patients often exhibit bias.^{2,6} Preliminary results from the embedded qualitative research study of audio recordings of the recruitment consultation have led to improvements by researchers in balancing the treatment arms and explaining equipoise. In parallel the NRG BN-003 study (<http://clinicaltrials.gov/ct2/show/NCT03180268>) will also provide class I evidence.

It is incumbent on the neurosurgery and oncology community to work collaboratively to ensure both trials are successfully delivered in order to establish the best way to manage patients with complete resection of WHO grade II meningioma.

Michael D. Jenkinson, FRCSEd, PhD^{1,2}

Damien C. Weber, MD³

Brian J. Haylock, FRCR⁴

Frances C. Sherratt, PhD⁵

Bridget Young, PhD⁵

Michael Weller, MD⁶

Helen Bulbeck, PhD⁷

Giovanna Culeddu, MSc⁸

Dyfrig A. Hughes, PhD⁸

Alice Brain, MSc⁴

Kumar Das, FRCR¹

Matthias Preusser, MD, PhD⁹

Priya Francis, BSc²

Carrol Gamble, PhD²

¹The Walton Centre NHS Foundation Trust, Liverpool, United Kingdom

²Institute of Translational Medicine, University of Liverpool, United Kingdom

³Center for Proton Therapy, Paul Scherrer Institute, Villigen, Switzerland

⁴Clatterbridge Cancer Centre, Wirral, United Kingdom

⁵Institute of Psychology, Health and Society, University of Liverpool, United Kingdom

⁶University Hospital Zurich, Switzerland

⁷braintrust charity, Cowes, Isle of Wight, United Kingdom

⁸Centre for Health Economics and Medicines Evaluation, University of Bangor, United Kingdom

⁹Comprehensive Cancer Centre Vienna, Medical University of Vienna, Austria

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Correspondence

Michael D. Jenkinson: michael.jenkinson@liv.ac.uk.

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Response

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